REMARKS/ARGUMENTS

Summary of Examiner Interview

Applicants thank Examiners Anderson and Spivack for the courtesies extended to Applicants' representatives John Kilyk, Jr., and Jennifer M. Duk during the telephone interview on April 4, 2007, at which time the obviousness rejections in the Office Action were discussed. Applicants' comments during the interview generally reflect the remarks/arguments herein.

The Pending Claims

Claims 8-14, 16, and 38-43 are currently pending. Reconsideration of the pending claims is hereby requested in view of these remarks/arguments.

Discussion of Claim Amendments Relative to Immediately Previous Claim Set

No claim amendments are made relative to the immediately previous claim set.

Discussion of Claim Amendments Relative to Issued Claims

Claim 8 has been amended to replace the term "pharmaceutically" with the term "physiologically." Claim 8 has been amended to recite that the "at least one compound is administered with" the pharmaceutically acceptable carrier. In addition, claim 8 has been amended to recite the phrase "wherein said at least one compound exhibits an overall effect of rotating the plane of polarized light in the (-) direction" for additional clarity. These claim amendments are supported by the specification at, for example, column 7, lines 29-66. In addition, claim 11 has been amended to recite a blood level of "200-1000 ng/dl" as supported by the specification at, for example, column 7, Table 4.

Claim 16 is a new claim depending from claim 8, which further recites that the cancer is a "carcinoid tumor of neuroendocrine tissue located in the lung, pancreas, or gastrointestinal tract." Support for new claim 16 is found in the specification at, for example, column 2, lines 20-25.

New claims 38-43 depend from claim 8 and mirror claim 10 except that the new claims individually recite ovarian, thyroid, testicular pituitary, prostate, and breast cancer, respectively. Support for new claims 38-43 is found in the specification at, for example, column 7, lines 29-34.

The amended claims and the newly added claims, therefore, narrow the scope of the issued claims, and no new matter has been added by way of these amendments.

The Office Action

Claims 8-10, 16, and 38-43 are rejected under 35 U.S.C. § 103(a) as allegedly unpatentable over Wu (*Cancer Research*, 49: 3754-3758 (1989)) in view of Band (*Gynecologic Oncologists*, 23: 261 (1986)), and Zhang (*Acta Academiae Medicinae Sinicae*, 7: 384-387 (1985)). Claims 11-14 are rejected under 35 U.S.C. § 103(a) as allegedly unpatentable over Wu, Band (1986), and Zhang in further view of Wu (*Clin. Pharmacol. Ther.* 39: 613-618 (1986)). Applicants traverse these rejections.

Discussion of Rejections Under 35 U.S.C. § 103

The Office Action contends that the subject matter of claims 8-16, and 38-43 would have been obvious to one of ordinary skill in the art at the relevant time in view of the combined disclosures of Wu (1989), Band (1986), Zhang, and Wu (1986).

It would not have been obvious to one of ordinary skill in the art that (-)-gossypol would be effective to treat cancer in humans based on the teachings of the cited references. Wu (1989) discloses the use of gossypol on cell lines *in vitro* and *in vivo* in mice. Wu (1986) discloses that gossypol has antispermatogenic activity and examines the pharmacokinetics of gossypol in humans and dogs. However, there is no teaching in Wu (1989) or Wu (1986) that gossypol is effective to treat cancer in humans.

Zhang discloses that (-)-gossypol is more effective than (+)-gossypol and racemic gossypol in the treatment of HeLa cells *in vitro*. There is no teaching in Zhang that (-)-gossypol is effective to treat cancer in humans.

Band (1986) discloses the *in vitro* testing of gossypol optical isomers on cell lines of ovarian and testicular cancer as well as mesodermal tumor of uterine origin. Further, Band (1986) discloses that (-)-gossypol is more potent than (+)-gossypol and may be clinically useful in the treatment of reproductive tract cancers. However, in a subsequent publication, Band restates the potency of (-)-gossypol relative to (+)-gossypol, and concludes that the anti-proliferative action of gossypol is non-selective, thereby making it lethal to normal, non-cancerous, reproductive tract cells (*Gynecologic Oncology*, 32: 273-277 (1989)).

This lack of specificity of (-)-gossypol is shown in other studies as well. Hu discloses that gossypol targets actively proliferating cells, regardless of normal or malignant origin (*In Vitro Cell Dev. Biol.*, 22(10): 583-588 (1986)). Tso discloses gossypol could be safely and effectively administered to mice within only a very narrow range (*Cancer Letters*, 24: 257-261 (1984)). Although a daily dosage of 25-100 μg of gossypol was found to be relatively safe and effective, with 100 μg being optimal, when the dosage was increased to 250 μg/day, all of the treated mice died due to gossypol toxicity. Thus, Tso discloses that at a dosage only 2.5 times the reported optimal therapeutic dosage, gossypol was lethal. In addition, Rao discloses that 34% of mice treated with an optimum dose of gossypol died of drug toxicity and that the survival rate decreased sharply at doses on either side of the optimum (*Cancer Chemother. Pharmacol.*, 15(1): 20-25 (1985)). Therefore, Rao states that mice given the suboptimal dose died as a result of the tumor and that mice given the optimal dose died of drug toxicity. Rao further discloses that rapidly proliferating mouse leukemias, P388 and L1210, failed to respond to gossypol.

Alone or in combination, Wu (1986 and 1989), Zhang, and Band fail to disclose the efficacy of (-) - gossypol in the treatment of cancer in humans. The teachings therein regarding *in vitro* testing and/or testing in mice would not have led one of ordinary skill in the art to reasonably expect that (-)-gossypol would be an effective treatment of cancer in humans, particularly in view of the teaching of non-selective cytotoxicity of gossypol in Band (1989), Hu, Tso, and Rao. Further, although the Office Action asserts that (+)-gossypol is the likely cause of gossypol toxicity, Wu (1986) points out that "only (-) – gossypol exhibited both efficacy and toxicity *in vivo*, whereas (+) – gossypol was inactive and of low toxicity." As stated in the Office Action, "*in vitro* and *in vivo* testing are established models for evaluating anticancer activity." Therefore, in view of the *in vitro* toxicity of gossypol to both cancerous and noncancerous human cells as reported by Band (1989), and given that gossypol was found by Rao and Tso to be lethal in mice at doses only marginally higher than the reported optimal doses, one of ordinary skill in the art would not only reasonably conclude that gossypol would be toxic to cancerous and noncancerous human cells *in vivo*, but also would not be motivated to try (-)-gossypol in the treatment of human cancer, let alone reasonably expect that it would be safe and effective to treat cancer in a human. Therefore, at the time the present invention was made, one of ordinary skill in the art would not have believed that it would be possible to determine successfully a safe and effective

dosage range in genetically heterogenous humans for a drug that displays such a general toxic effect *in vitro*, and such a narrow window of efficacy and safety in a genetically homogenous population of in-bred rodents (see Declaration of Dr. Marcus Reidenberg, dated May 12, 2005).

The Office Action states that the totality of the prior art renders the invention obvious. However, the Office is impermissibly using hindsight in this determination. At the time the application was filed, *the totality of the art* would not have even led one of ordinary skill in the art to try to administer (-) –gossypol to a human for the treatment of cancer. As none of the references cited in the Office Action demonstrates the efficacious use of (-)-gossypol in the treatment of cancer in humans, and in view of the lack of selectivity of gossypol discussed in Band (1989), Hu, Tso, and Rao, one of ordinary skill in the art would not have had a reasonable expectation of success in treating cancer in humans with (-)-gossypol. In view of the foregoing, the subject matter of the pending claims would not have been obvious to one of ordinary skill in the art at the time of the filing of the relevant application. Therefore, Applicants respectfully request that the rejection be withdrawn.

Conclusion

The application is considered in good and proper form for allowance, and the Examiner is respectfully requested to pass this application to issue. If, in the opinion of the Examiner, a telephone conference would expedite the prosecution of the subject application, the Examiner is invited to call the undersigned attorney.

Respectfully submitted,

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